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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 2004/004718 A1**

(54) Title: **LIQUID DOSAGE FORMS OF ACID LABILE DRUGS**

(57) Abstract: Liquid formulations of acid-labile drugs are provided. The formulations generally comprise micro-granules comprising an acid-labile drug coated with an enteric coating and a liquid vehicle having a pH less than 6.0. The components of the formulation can separately provided in the form of kits. The formulations and kits may be used to treat patients suffering from disorders for which the acid labile drugs are indicated.

## **LIQUID DOSAGE FORMS OF ACID LABILE DRUGS**

### **Technical Field**

The present invention relates to liquid dosage forms and in particular, relates to liquid dosage forms of acid labile drugs.

### **Background of the Invention**

Many pharmaceutical compounds are susceptible to degradation in acidic environments. For example, antibiotics such as erythromycin; proton pump inhibitors (or "PPIs") such as Lansoprazole®, or Omeprazole®; and pencreatin; are compounds that degrade in acidic environments and are therefore referred to as "acid labile". Oral delivery of acid labile pharmaceutical compounds is challenging because the gastric pH is very acidic (typically between about pH 1.5 and 1.9). Under such conditions, acid-labile drugs typically degrade and are not readily available for uptake without being protected.

Due to the pH sensitivity of acid labile drugs, they typically are administered in a form that protects the drug from the acidic gastric environment. Enteric coatings are probably the most widely used method of protecting acid-labile drugs from gastric degradation. Enteric coating methods typically form a barrier around drug particles, or an entire dosage form containing an acid-labile drug, with a coating that does not dissolve upon introduction to the low pH of the gastric environment. Such enteric coatings typically dissolve at a pH greater than 6, such as that found in the upper small intestine where the acid labile drugs are released in an environment where they will not significantly degrade, and therefore can be absorbed. Unfortunately, enteric coated compositions are difficult to formulate as liquids, thus creating difficulty in administration to pediatric patients, patients having difficulty swallowing, or patients who cannot swallow at all such as when critically ill patients are fitted with a naso-gastric tube or a gastronomy tube (variously and collectively referred to as an "NG-tube") for feeding.

Notwithstanding the above, attempts have been made for formulate liquid dosage forms of acid-labile drugs. For example, U.S. Patent No. 5,840,737 recommends dissolving the contents of commercially available capsules containing enterically coated

pellets of a PPI in a solution of sodium bicarbonate buffer. In practice, the above method requires a practitioner to open a capsule and release the enterically coated PPI into the buffer. After the contents of the capsule and buffer are combined, the mixture is swirled or mixed for approximately 20 to 30 minutes so that the enteric coating dissolves in the buffer's relatively high pH. Once the enteric coating is dissolved, the PPI is relatively stable in the buffer and is able to be administered to a patient. However, the volume of buffer used in this practice is relatively large and can produce stomach gases and therefore belching which is detrimental to individuals suffering from gastro-esophageal reflux disease (GERD), one of the disease states a PPI is intended to alleviate.

Additionally, the buffer employed typically is a separate component that adds to the cost of providing such a formulation. Additionally, when given orally, the taste of such a solution is unpleasant. Also, great care must be taken to completely dissolve the enteric coating layer from the enterically coated PPI since undissolved components of an enteric coating layer tend to form sticky globules that can stick together or stick to the walls of an NG-tube, for example.

There is therefore a need for a liquid dosage form for acid-labile drugs that maintains the efficacy of the active component, is easily administered to patients in a low volume of liquid, and is palatable.

## **Summary of the Invention**

In accordance with the present invention, liquid formulations of acid-labile drugs are provided that maintain the efficacy of the acid-labile drug, are easy to use and may be administered in relatively small volumes. The formulations generally comprise micro-granules comprising an acid-labile drug coated with an enteric coating and a liquid vehicle having a pH less than 6.0. The components of the formulation can be separately provided in the form of kits. The formulations and kits may be used to treat patients suffering from disorders for which the acid labile drugs are indicated.

## **Detailed Description of the Invention**

The present invention provides a liquid formulation of an acid labile drug that generally is simple to formulate and cost efficient. The formulation can be provided in relatively small volumes that are easily swallowed or administered through an NG-tube with little, if any, need for rinsing or flushing to provide a patient with a complete dose of an acid labile drug. As a result, patients are not provided with unnecessary liquids

that, as mentioned above, can be contraindicated for certain patients. Additionally, the compositions provided herein are relatively quickly formulated.

Generally, the formulation comprises micro-granules of an enterically coated acid-labile drug and a liquid vehicle having a pH that will not dissolve the enteric coating, typically a pH of less than 6.0. The micro-granules typically will comprise an acid-labile drug protected by an enteric coat. Any acid-labile drug is suitable for use in the present invention and include, but are not limited to certain antibiotics such as erythromycin; proton pump inhibitors (or "PPIs") such as, for example, Lansoprazole®, omeprazole®, and pantoprazole; and penicillin. Such drugs may be formulated with other active or inactive ingredients before being enterically coated. For example, stabilizers such as salts of group I or group II metals such as, for example, magnesium oxide, magnesium hydroxide, calcium carbonate, or sodium bicarbonate may be used in such formulations to maintain the integrity of the active drug; fillers such as talc; as well as sugars and other excipients such as sucrose, mannitol, and microcrystalline cellulose, may also be part of such formulations.

Micro-granules will also comprise a therapeutically effective amount of an acid-labile drug. A "therapeutically effective amount" as used herein means a sufficient amount of, for example, the composition, compound, or formulation necessary to treat the desired disorder, at a reasonable benefit/risk ratio applicable to any medical treatment. As with other pharmaceuticals, it will be understood that the total daily usage of a pharmaceutical composition of the invention will be decided by a patient's attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and other factors known to those of ordinary skill in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Formulations of the invention are administered and dosed in accordance with sound medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners.

5 Therapeutically effective amounts for purposes herein thus can readily be determined by such considerations as are known in the art. The amount must be affective to achieve improvement, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusions, improved survival rate, more rapid recovery, and/or improvement/elimination of symptoms and  
10 other indicators as are selected as appropriate measures by those skilled in the art.

Those skilled in the art will recognize that the micro-granules may also comprise multiple coatings. Coatings, in addition to the enteric coat, may be applied to the core formulation prior to applying the enteric coating layer. Additional coatings typically are employed to protect the acid labile drug in cases where it may react with the enteric  
15 coating material. Hence, the additional coating(s) may be applied between the acid labile drug core and the enteric coat. Materials that typically are employed for this purpose include, but are not limited to hydroxy propyl cellulose and hydroxy propyl methyl cellulose (HPMC). The use of additional coating layers in a micro-granule is largely a matter of choice for those skilled in the art based upon the composition of the acid labile  
20 drug and enteric coating material employed. Such determinations are routinely made empirically by performing side-by-side stability studies on enterically coated micro-granules having sub-coatings and similarly composed micro-granules without sub-coatings.

Enteric coatings and methods for applying enteric coats are well known in the art.  
25 Enteric coatings generally comprise ingredients that do not dissolve in environments having a pH less than 6.0. Typically, enteric coatings of the present invention will protect the acid-labile drug in the pH of the liquid composition as well as the gastric environment. Any of the well known enteric coating materials are suitable for use with the present invention and may include polymers of compounds such as, for example,  
30 stearic acid, palmitic acid, and behenic acid; and polymers like hydroxy propyl methyl cellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, methacrylic acid copolymers and cellulose acetate trimellitate.

Microgranules may take many different forms depending upon the granulation and sieving procedures employed but typically are, for the most part, spherical in nature and have a size range of between 100  $\mu\text{m}$  and 900  $\mu\text{m}$ , more preferably between 100  $\mu\text{m}$  and 700  $\mu\text{m}$ , and most preferably between 200  $\mu\text{m}$  and 500  $\mu\text{m}$ .

5 Liquid vehicles that may be employed according to the present invention may inherently have a pH of less than 6.0 or additional ingredients such as acidic excipients may be added to a liquid vehicle to achieve a pH of less than 6.0. Citric acid and ascorbic acid are suitable for maintaining the pH of liquid below 6.0. Typically, the pH of the liquid vehicle is less than 6.0, preferably less than 5.5, more preferably less than 5.5, and most preferably less than 5.0.

10 Due to the nature of the present formulation the volume of the liquid vehicle employed can be extremely variable. While there is no upper limit to the volume of the liquid vehicle employed, practical considerations (as mentioned above) show the need for a low volume formulation. Advantageously, the present formulation can be administered in relatively low volumes. Typically, the volume of the liquid vehicle employed is less than 50 ml, preferably less than 25 ml and most preferably less than 10 ml. In most cases, the volume of the liquid vehicle will be at least 0.5 ml, more preferably at least 2.0 ml, and most preferably at least 5.0 ml.

Many configurations for the compositions are possible. For example, the micro-  
20 granules can be formulated into a fast dissolving tablet such as those found in U.S. Patent Numbers 5,464,632 and 6,299,904 which are herein incorporated by reference. Such tablets may also contain an acidic excipient such that when the tablet is placed in water the micro-granules and acidic excipient are released. As a result, the acidic excipient produces a liquid having a pH of less than 6.0 that also contains the micro-granules.  
25 Alternatively, sachet formulations are also suitable for producing a composition comprising micro-granules and a liquid vehicle having a pH of less than 6.0. Sachets typically are packaged dry ingredients which, for present purposes, could contain enterically coated micro-granules of a acid labile drug and an acidic excipient. Similarly to a fast dissolving tablet, such a sachet formulation simply could be placed in small  
30 volume of water to form a composition comprising micro-granules and a liquid vehicle having a pH of less than 6.0. Of course, other ingredients such as flavoring agents, surfactants, sweeteners, as well as other well known excipients could be added to such formulations.

The compositions of the present invention may be provided as kits containing separately packaged containers of the components of the composition. For example, a kit may contain a vial of water and a tablet containing dry ingredients of the formulation such as the enterically coated micro-granules and an acidic excipient. Upon transferring the tablet in the water provided, a liquid formulation is formed. It will be understood of course that the composition may come as separate components, but the separate components should be mixed to form a liquid formulation comprising the microgranules in a liquid vehicle having a pH such as those specified above, prior to administration. In cases where kits are provided, the kits may come with instructions for appropriate mixing of the dry and liquid components. Additionally, it is preferable that the dry ingredients completely disperse in the liquid ingredients in less than 10 minutes, preferably in less than 5 minutes, and most preferably in less than 2 minutes.

Preferably, compositions of the present invention comprising a PPI are provided to patients experiencing gastrointestinal disorders such as, for example, acid reflux disease, gastro-esophageal reflux disease, acid related gastrointestinal disorders such as peptic and duodenal ulcers, Zollinger Ellison Syndrome, or any other gastrointestinal disorder for which PPI's are indicated to thereby alleviate such disorders. The formulations are particularly well suited for patients outfitted with an NG-tube. It has been discovered that micro-granules flow freely and relatively completely through a patient's NG-tube without rinsing for purposes of insuring that the patient receives a complete dose of a prescribed medication. Hence, methods are provided for treating gastrointestinal disorders comprising administering a composition of the present invention comprising a PPI to a patient in need of such a therapy such as those experiencing gastrointestinal disorders.

## Examples

### Example 1

#### Passage of Micro-granules Through Small Orifice

5           This experiment demonstrates that the Lansoprazole® micro-granules from a Lansoprazole® fast dissolving tablet ("LFDT"; TAP Pharmaceutical Products Inc., Lake Forest, IL) can pass through an orifice that is less than 2 mm in diameter. LFDT tablets contain enterically coated micro-granules of lansoprazole® that are about 350 microns in size. The tablets also comprise citric acid as an acidic excipient that is sufficient to lower  
10   the pH of 30 ml of water to less than 5.0.

          An LFDT (30 mg) was placed in a 20 cc syringe from which the plunger had been removed. The plunger was replaced and the needle was uncapped. About 5 cc of sterile water for injection (SWFI) was drawn into the syringe. The syringe was gently shaken for about 45 seconds to ensure that the LFDT dissolved and formed a suspension.  
15   The contents of the syringe were injected into an empty flask. The syringe was examined for any residual contents. The contents of the flask were analyzed by HPLC. According to the HPLC analysis, greater than 95% of the drug was recovered in the flask, indicating that the micro-granules from LFDT freely passed through the orifice of the syringe.

20

### Example 2

#### Stability of Micro-granule Compositions in Different Acidic Liquid Vehicles

          This example demonstrates the stability of enterically coated microgranules in various liquid vehicles. The liquid vehicles employed in this experiment were SWFI and  
25   apple juice. After dissolution of LFDT tablets in the various liquid vehicles, the suspensions were added to simulated gastric fluid, or "SGF", containing 2.0 gm NaCl and 7 ml of HCl/1000ml of water. The ability of the micro-granules to protect the active ingredient Lansoprazole® was determined over time.

          5.0 ml of SWFI was pulled into a 10 ml syringe containing a LFDT tablet. The  
30   syringe was tapped and gently swirled for approximately 45 seconds. The contents of the syringe were then delivered into a flask containing 50.0 ml of SGF. 5.0 ml of additional SWFI was pulled into the syringe and briefly swirled before the contents were placed in the flask containing the SGF. The flask was then allowed to sit for 30 minutes



with gentle swirling at five minute intervals. 5.0 ml of 2N NaOH then was added to the flask after the 30 minute time period and the contents of the flask was diluted to 100 ml with pH 10 buffer (60:40:1 water:acetonitrile (ACN):triethylamine (TEA) pHed with  $H_3PO_4$ ). The addition of the high pH buffer and NaOH increased the pH such that the enteric coating of the Lansoprazole® micro-granules dissolved and released the Lansoprazole® into the high pH buffer in which Lansoprazole® is stable. 5.0 ml of the solution from the flask was diluted with a further 25.0 ml of the pH 10 diluent. The diluted sample was then filtered through a 0.45µm filter. The first 2.0 ml of filtrate was discarded and a 1.5 ml sample of the remaining filtrate was tested by HPLC for the presence of Lansoprazole®.

The procedure above was repeated except that the SWFI was replaced with apple juice having a pH of 3.9.

HPLC analysis on the above samples showed that after 30 minutes of suspension in SWFI or apple juice, 96.6% and 96.3% of the Lansoprazole® in the micro-granules respectively was recovered. Hence, the enteric coating on the micro-granules was stable in the acidic environments.

### Example 3

#### Stability of Microgranules in Acidic Liquid Vehicle

This example demonstrates that micro-granules of Lansoprazole® (present in LFDT) are stable when LFDT is dissolved in water and held for 20, 30 and 60 minutes.

10.0 ml of SWFI was placed into each of three 30 ml beakers. A LFDT was placed into each of the beakers containing SWFI. After 20 minutes one beaker containing LFDT in SWFI was poured into a flask containing 490 ml of 0.1 N HCl warmed to 37°C. Prior to combining the contents of the beaker and flask, 10 ml of the 0.1 N HCl was removed from the flask and used to rinse the beaker containing the LFDT. Upon rinsing the beaker, the contents were returned to the flask. This procedure was repeated for the other beakers after 40 and 60 minutes.

After the contents of the beakers were added to the flasks containing the warm 0.1N HCl, the samples were allowed to incubate for 60 minutes at 37°C with constant stirring using a paddle on a motor set to rotate at 75 rpm. After the incubation times, 25 ml of the contents of the flasks were removed and 25 ml of 2N NaOH was then added to the flasks which increased the pH of the flasks to between 11 and 12 as determined with pH

0-14 pHing paper. Upon addition of the 2N NaOH, the rpm of the paddle was increased to 200 rpm and allowed to mix the samples for an additional 60 minutes. The addition of 2N NaOH dissolves the enteric coating and provides an environment where Lansoprazole® is stable. 10 ml aliquots of the flasks were then removed and filtered through a 45 µm filter. The first 2-3 ml of the filtrates was discarded and the remaining portion was used for HPLC analysis. HPLC was used to determine the amount of Lansoprazole® recovered from the final flasks. The percent of Lansoprazole® recovered is shown in Table 1 below over the time periods tested.

Table 1

Time in SWFI, prior to 1hr. in 0.1N HCl (minutes)	% of lansoprazole® remaining <b>LFD</b>
20	92
40	90
60	88

As shown by Table 1, the LFD formulation protected Lansoprazole® for extended periods of time when exposed to water prior to contact with acid

#### Example 4

##### Acidic Buffering Capacity of LFD

This example was designed to determine the effects of water volume on the pH of a solution containing the water and an LFD.

One LFD tablet was dispensed in to vials containing 1, 2, 3, 4, 5, 10, 20, and 30 ml of SWFI. The vials were gently swirled until the LFD was completely disintegrated. The pH's of the vials was then measured 2-3 minutes after the LFDs were completely disintegrated with an Accumet Model 915 pH meter equipped with pencil epoxy electrode. The disintegration time and pH of the various suspension is shown in Table 2 below.

Table 2

Volume of SWFI (ml)	Time to disintegrate (seconds)	pH
1	60	3.77
2	45	3.84
3	45	3.95
4	35	3.99
5	40	4.01
10	45	4.06
20	40	4.13
30	35	4.18

- LFDt tablets can be dissolved in a wide variety of volumes of SWFI, while maintaining the pH of the resulting suspension below 4.5.

#### Example 5

##### NG-tube Administration of Liquid Dosage Forms

- This experiment analyzed the volume of liquid used to pass micro-granules from LFDt through a NG-tube.

- An LFDt tablet was dispensed into two separate 35 ml catheter-tipped syringes. 10 ml of apple juice was added to one syringe and 10 ml of distilled water was added to the other syringe and both syringes were shaken. The contents of the syringes were then delivered to separate NG-tubes that were configured in a manner designed to mimic the curvation and length of a NG-tube in an actual patient. The contents of the liquid flowing through the NG-tube were collected in a flask attached at the opposite end of the NG-tube. The syringes were then rinsed once with 10 ml of the suspension liquid (i.e. either apple juice or distilled water). The rinse fluid was transferred to the NG-tube and collected in the flask as above. Accordingly, a total of 20 ml of liquid was transferred through the NG-tube.

The 20 ml samples collected from the NG tubes were combined with 1.0 ml of 2N NaOH and mixed well before an additional 30 ml of 0.1N NaOH were added to the

samples. The contents of the flasks were then diluted to 100 ml with ACN and mixed well. 10.0 ml of this solution was then diluted to 50.0 ml with pH 10 diluent (2400 ml HPLC grade water, 1600 ml of HPLC grade ACN, 40 ml HPLC grade TEA, pHed to 10.0 with H<sub>3</sub>PO<sub>4</sub>). A portion of this solution was then filtered through a 0.45 µm filter.

- 5 The first 2 ml of filtrate was discarded and the next 1.5 ml was collected for HPLC analysis to determine the amount of Lansoprazole® recovered at the end of the NG-tube. The results of the HPLC analysis is shown in Table 3 below.

Table 3

<b>Test Sample</b>	<b>Gastrostomy tube size</b>	<b>Total volume of suspending vehicle</b>	<b>% Lansoprazole® recovered through tube using Distilled Water</b>	<b>% Lansoprazole® recovered through tube using Apple Juice</b>
LFDt tablets	12 F	20 mL	100.1	97.9

10

As shown in Table 3, 100.1% and 97.9 % of Lansoprazole® was recovered when the LFDt micro-granules were administered through a 12 F NG-tube utilizing distilled water and apple juice, respectively. These results demonstrate the benefit of administering micro-granules via a gastrostomy tube.

15

While the invention has been described in detail and with reference to specific embodiments, it will be apparent to one skilled in the art that various changes and modifications may be made to such embodiments without departing from the spirit and scope of the invention.

20

**Claims:**

- 5 What is claimed is:
1. A pharmaceutical formulation comprising:
    - (a) micro-granules comprising an acid-labile drug coated with an enteric coating; and
    - 10 (b) a liquid vehicle having a pH less than 6.0.
  2. The composition of claim 1 wherein the micro-granules are between 100  $\mu\text{m}$  and 900  $\mu\text{m}$ .
  - 15 3. The composition of claim 1 wherein the acid labile drug is a proton pump inhibitor.
  4. The composition of claim 3 wherein the proton pump inhibitor is Lansoprazole®.
  - 20 5. The composition of claim 1 wherein the liquid has a volume of less than 50 ml.
  6. A method of treating a patient with a gastrointestinal disorder comprising providing to the patient a composition comprising micro-granules of an enterically coated proton pump inhibitor and a liquid vehicle having a pH less than 6.0.
  - 25 7. A kit comprising:
    - a) a first container comprising micro-granules comprising an acid labile drug coated with an enteric coating; and
    - b) a second container comprising a liquid vehicle;
    - 30 wherein the first or the second container further comprises an acidic excipient.
  8. The kit of claim 7 wherein the acid-labile drug is a proton pump inhibitor.
  9. The kit of claim 8 wherein the proton pump inhibitor is Lansoprazole®.
  - 35 10. The kit of claim 7 wherein the micro-granules are between 100  $\mu\text{m}$  and 900  $\mu\text{m}$ .
  11. The kit of claim 7 wherein the volume of the liquid vehicle in the second container is less than 50 ml.
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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 03/20875

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4439 A61K9/08 A61K9/10 A61K9/58 A61K9/26

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 731 002 A (PILBRANT ANGSTROM KE GUNNAR ET AL) 24 March 1998 (1998-03-24) column 1, line 65 -column 4, line 29 column 4, line 58 -column 5, line 2 example 2	1-11
X	US 6 132 770 A (LUNDBERG PER JOHAN) 17 October 2000 (2000-10-17) column 3, line 21 - line 55 column 3, line 61 -column 4, line 8 column 7, line 41 -column 8, line 6 examples	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

29 September 2003

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10/10/2003

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/20875

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 299 904 B1 (SHIMIZU TOSHIHIRO ET AL) 9 October 2001 (2001-10-09) cited in the application column 4, line 26 - line 59 column 5, line 44 - line 61 column 6, line 16 - line 17 example 5 -----	1-11
X	US 6 328 994 B1 (SHIMIZU TOSHIHIRO ET AL) 11 December 2001 (2001-12-11) examples -----	1-11
Y	US 5 464 632 A (BRUNA ETIENNE ET AL) 7 November 1995 (1995-11-07) cited in the application abstract column 1, line 12 - line 60 column 3, line 41 - line 51 examples -----	1-11
Y	WO 02 45692 A (BYK GULDEN LOMBERG CHEM FAB ;LINDER RUDOLF (DE); DIETRICH RANGO (D) 13 June 2002 (2002-06-13) page 3, paragraph 3 -page 5, paragraph 1 page 9, paragraph 1 -page 10, paragraph 2 examples D,E -----	1-11
Y	WO 00 74654 A (BYK GULDEN LOMBERG CHEM FAB ;LINDER RUDOLF (DE); DIETRICH RANGO (D) 14 December 2000 (2000-12-14) examples C,E -----	1-11
Y	US 4 786 505 A (ODA MINORU ET AL) 22 November 1988 (1988-11-22) the whole document -----	1-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/20875

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1 partially  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 6

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1 partially

Present independent claims 1 and 7 relate to an extremely large number of possible compositions, namely a pharmaceutical formulation comprising enterically coated microgranules of an acid labile drug, and a liquid vehicle having a pH of less than 6, with no limitation or restriction as to the acid labile drug or as to the liquid carrier.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed, namely those wherein the acid labile drug is a proton pump inhibitor (PPI) within the meaning of claims 3 and 4. Compositions comprising acid labile drugs other than PPI, even if mentioned in the description, cannot be considered to be sufficiently disclosed. As to the liquid carrier, the application discloses only aqueous solutions comprising acidic excipients such as citric acid. Other ways of solving the relevant technical problem are not shown by means of evidence in the application.

In the present case, therefore, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compositions comprising enterically coated PPI microgranules and an acidic excipient as defined in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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